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CAMPBELL & FLORES LLP
4370 LA JOLLA VILLAGE DRIVE
7TH FLOOR
SAN DIEGO, CA 92122

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Paper No. 81

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Serial Number: 08/349,479
Filing Date: December 2, 1994
Appellant(s): Border and Ruoslahti

Astrid Spain
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's Brief on appeal filed 3/11/02 (Paper No. 80).

The text of those sections of Title 35 U.S. Code not included in this appeal can be found in a previous Office Action herein.

(1) Real Party of Interest.

A statement identifying the real party of interest in contained in the Brief.

(2) Related Appeals and Interferences Identified.

A statement identifying that no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the Brief.

(3) Status of Claims.

The statement of the status of claims contained in the Brief is correct.

This appeal involves claims 21-23 and 25 set forth in Appendix A.

(4) Status of Amendments After Final.

The appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

It is acknowledged that examiner and appellant discussed whether appellant's splitting Markush-type claim 23 into two separate claims, amended claims 23 and new claim 35, each directed to a single species, raised new issues by introducing new claim elements or limitations.

Appellant and examiner discussed that the only issue in the appeal was one of priority.

The Advisory Action, mailed 5/14/01 (Paper No. 71), indicated that the After Final Amendment, filed 3/15/01 (Paper No.) would be entered.

However, as indicated previously in Paper No. 78, appellant's after final amendment, filed 10/18/01 (Paper No. 76), was not entered as it raised new issues and consideration.

Therefore, this appeal involves claims 21-23 and 25 set forth in Appendix A.

(5) Summary of Invention.

The summary of invention contained in the Brief is correct.

(6) Issues.

The appellant's statement of the issues in the Brief is correct.

It is acknowledged that appellant and the examiner agree that the only issue addressed in the Appeal Brief, filed 10/15/01 (Paper No. 75), and reiterated herein in the Appeal Brief, filed 3/11/02 (Paper No. 80), is the priority of the invention as set forth in Section VI of the Brief. Therefore, the previous Appeal Brief, filed 10/15/01, was not defective.

For the record, appellant has maintained that the after final amendment splitting Markush-type claim 23 into two separate claims, did not raise new issues by introducing new claim elements or limitations.

However, appellant's arguments appear to rely on issues associated with distinguishing the species and the prior art rejection of record. For example page 20, paragraph 1 of the Appeal Brief respectfully submits that the ARDS species is not anticipated by Dasch et al. Therefore, if claims in Appendix B were the claims under consideration, then Dasch et al. would not meet claim 23. However, given that the claims in Appendix A are under consideration, then Dasch et al. does meet claims.

(7) **Grouping of Claims.**

Appellant's Brief includes a statement that claims do not stand or fall together. However, appellant's statement in the Brief that certain claims do not stand or fall together is not agreed with because of the reasons of record and set forth herein. Both appellant and examiner have prosecuted the claims as if they stood or fell together. The only issue of record has been whether appellants' Declaration under 37 C.F.R. 1.13, filed on March 15, 2001 was sufficient to antedate U.S. Patent No. 5,772,998.

On page 17, paragraph 1 on the Appeal Brief, appellant asserts that in order to antedate a reference that has been cited against an application, distinct requirements exist that depend, in part, on whether the application claims a genus or species and, in part, on the species disclosed in the cited references. Consequently, claims 21-23 and 25 must be separately examined with regard to whether appellant have made the necessary showing for prior invention of the claimed subject matter It is for this reason, claim 21, directed to a genus, and claims 22, 23, 25 and if entered, claim 35 each directed to distinct species, do not stand or fall together.

Generic claim 21 recites "a method of decreasing the deleterious accumulation of extracellular matrix associated with a pathology or a condition wherein TGF-β-induced production and deleterious accumulation of extracellular matrix comprising contacting the tissue with an anti-TGF-β antibody that bind to TGF-β".

However, appellant was not in possession of the generic invention prior to the effective date or activity of the prior art. The Rule 131 Declaration and corroborating evidence does not provide the minimum disclosure required for the given scope of "pathologies and conditions" to antedate the prior art. A reference or activity which discloses several species of a claimed genus can be overcome directly under 37 CFR 1.131 only by a showing the applicant completed, prior to the date of the reference or activity, all of the species shown in the reference. In re Stempel, 113 USPQ 77 (CCPA 1957). See MPEP 715.03(B).

Given the scope as well as the recitation of "pathology and condition" recited in the independent claim as well as the dependent claims, the claims are not simply directed toward suppressing the activity of "the deleterious accumulation of TGF-β-induced extracellular matrix in the tissue". Rather, the recitation of "pathology and condition" clearly indicates the context of multiple diseases or condition and determining which ones (or at least a representative number of species) are relevant or appropriate to the ordinary artisan.

Again, both appellant and examiner have prosecuted the claims as if they stood or fell together. The only issue of record has been whether appellants' Declaration under 37 C.F.R. 1.13, filed on March 15, 2001 was sufficient to antedate U.S. Patent No. 5,772,998. Appellant did not appear to distinguish the genus and species claims prior to this Appeal Brief.

(8) Claims Appealed.

The copy of the appealed claims contained in Appendix A to the Brief is correct.

(9) Prior Art of Record.

A) Bassols et al., J. Biol. Chem. 263: 3039-3045 (1988).
B) Dasch et al., U.S. Patent No. 5,772,998.
C) Ruoslahti et al., (U.S. Patent No. 5,583,103.

(10) Grounds of Rejection.

The following ground(s) of rejection are applicable to the appealed claims.

Rejection Under 35 U.S.C. § 102(e)

Claims 21, 23 and 25 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Dasch et al. (U.S. Patent No. 5,772,998; 1449). Dasch et al. teach the use of TGF-β-specific antibodies to neutralize the effects of TGF-β, including lung fibrosis, liver cirrhosis, fibrotic skin disorders and scarring (see entire document, including columns 5-6 and the Claims). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to treat lung fibrosis, liver cirrhosis, fibrotic skin disorders and scarring with TGF-β-specific antibodies. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993) for the inherency of methods.

Rejection Under 35 U.S.C. § 103

Claims 21-22 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Dasch et al. (U.S. Patent No. 5,772,998) in view of Ruoslahti et al. (U.S. Patent No. 5,583,103) AND/OR Bassols et al. (J. Biol. Chem. 263: 3039-3045, 1988).

Dasch et al. teach the use of TGF-β-specific antibodies to neutralize the effects of TGF-β, including lung fibrosis, liver cirrhosis fibrotic skin disorders and scarring (see entire document, including columns 5-6 and the Claims). Dasch et al. differs from the claimed methods by not disclosing that TGF-β was responsible, at least in part, for glomerulonephritis.

Ruoslahti et al. teach that it was known that excessive accumulation of extracellular matrix in glomerulonephritis was a diseases with a detrimental involvement of TGF-β (see column 2, paragraph 1) and that by treating TGF-β regulated activities, one treats certain pathologies including fibrotic disease and glomerulonephritis (see columns 5-6, overlapping paragraph). Further, Ruoslahti et al. teach that TGF-β-specific antibodies were able to inhibit the activity of TGF-β (see column 13)

Bassols et al. teach TGF-β regulates the expression of the extracellular matrix chondroitin/dermatan sulfate proteoglycans (see entire document, including Abstract, pages 3041 and 3043). Also, Bassols et al. teach that TGF-β regulates proteoglycans in kidney and lung and that TGFβ induces kidney fibroblast proliferation (see pages 3040-3041).

Given the teachings of Dasch et al. that TGF-β-specific antibodies could neutralize the effects of TGF-β in a several disorders; the one of ordinary skill in the art at the time the invention was made would have motivated to apply such TGF-β-specific antibodies in other disorders where TGF-β- played a role such as glomerulonephritis, as taught and indicated by Ruoslahti et al. and Bassols et al. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(11) Response to Argument

Rejections Under 35 U.S.C. §§ 102(e), 103

Appellant's arguments have been fully considered but are not found persuasive essentially for the reasons of record.

Appellant maintains the Border/Ruoslahti declarations under 37 C.F.R. § 1.131 sufficiently show that appellant's prior invention antedates the effective filing date of Dasch et al..

It is acknowledged that claim 21 is a genus claim directed to a method of decreasing the deleterious accumulation of extracellular matrix associated with a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of extracellular matrix in a tissue and that the dependent claims 22, 23 and 25 are species claims that recite the specific pathologies of glomerulonephritis, adult respiratory distress syndrome, liver cirrhosis and scarring.

Appellant acknowledges that Dasch et al. describe methods of neutralizing the inhibitory effects of TGF-β and several species of pathologies, including interstitial lung fibrosis, liver cirrhosis, fibrotic skin disorders such as scleroderma and scarring. In addition to the disclosure of Dasch et al., it is noted that Dasch et al. claims methods of neutralizing the inhibitory effects of TGF-β with TGF-β-specific antibodies

Appellant relies upon the averment by Border and Ruoslahti, pursuant to 37 C.F.R. § 1.131, that they conceived, prior to December 22, 1988, the claimed methods of decreasing TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology or a condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scarring, by contacting the affected tissued with anti- TGF-β antibody.

In response to the lack of supporting evidence or exhibits to show conception of all claim elements, appellant asserts that the controlling case law indicated that not every claim element needs to be supported by accompanying Exhibits, provided that any missing element is supported by the Declaration itself.

Appellant asserts that there exists no requirement to produce additional exhibits as appellant's reliance on the averments set forth in the Rule 131 declaration itself is entirely appropriate to establish conception of the invention prior to the effective date of the references. See Ex parte Ovshinsky, 10 USPQ2d (Bd. Pat. App. & Inter. 1989).

Appellant acknowledges that the MPEP states that the evidence in the form may accompany the declaration, but does not require such extrinsic evidence. See MPEP 715.07.

With respect to Ex parte Swaney, 89 USPQ 618 (Bd. Pa. App. & Int. 1951), appellant asserts that the conformity with the Swaney fact pattern has not been articulated by any court in the country.

Appellant maintains that no court has held that in order to show conception prior to a critical date, an applicant has to provide one or more exhibits that explicitly or implicitly contain all elements of the claimed invention.

Appellant further argues that the declaration under 37 C.F.R. § 1.131 as well as a corroborating third party Declaration under 37 C.F.R. § 1.132, filed 3/15/01 (Paper No. 69), contains additional averments with regard to the claimed species with regard to conception of the claimed methods prior to December 22, 1988 or appellants' due diligence in pursuing reduction to practice of the claimed methods during the critical period. See Exhibits A-E.

Appellant asserts that appellant's statements are corroborated by Languino's (Exhibit A) averment that they conceived, prior to December 22, 1988, the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology or a condition by contacting the affected tissue with an anti-TGF-β antibody.

Appellant relies upon the corroboration by Languino, who states that the during the time period Border conducted research related to the above-identified patent application in the same laboratory that the stated goal of using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix associated with a disease, including kidney disease.

It has been acknowledged the current Border/Ruoslahti declaration under 37 C.F.R. § 1.131 and Languino declaration under 37 C.F.R. § 1.132 set forth that the stated goal of preparing anti-TGF-β antibodies was for their use to inhibit TGF-β in order to decrease deleterious TGF-β-induced production and accumulation of extracellular matrix associated with a pathology or condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the lung and scarring.

Appellant relies upon that the Rule 131 Declaration itself that the stated goal of preparing anti-TGF-β antibodies was for their use to inhibit TGF-β in order to decrease deleterious TGF-β-induced production and accumulation of extracellular matrix associated with a pathology or condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the lung and scarring.

Other than the Rule 131 and 132 Declarations, neither Appellant or Languino have provided any corroborating factual evidence to support the "stated goals" using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix associated with a disease, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scarring, by contacting the affected tissued with anti- TGF-β antibody.

Appellant relies upon the "Animal Usage Form" (the redacted date of which is prior to December 22, 1998), which relates to the project entitled "Anti-human TGF-β Cyclic Peptide", which lists appellant Border and (non-co-inventor) Languino (but does not list not co-inventor Ruoslahti) as the investigators.

It is noted that Exhibit B to appellant's Rule 131 Declaration consists of laboratory notebook pages from (non-co-inventor) Languino's notebook to show the protocol of developing rabbit anti-TGF-β antiserum. The animals were for bled for anti-TGF-β antiserum December 13, 16 and 21 of 1988.

It is noted that the priority date of Dasch et al. (U.S. Patent No. 5,772,998) is December 22, 1988, which is one day after the final bleeding of the rabbits in the protocol of developing rabbit anti-TGF-β antiserum. Therefore, it appears that the rabbit anti-TGF-β antiserum was not tested prior to the effective priority date of Dasch et al. (U.S. Patent No. 5,772,998).

Appellant further relies upon Exhibit C, which is a conference abstract published for the Meeting of the American Society of Nephrology in San Antonio, Texas, which took place from December 11-14, 1988. This abstract is entitled "Transforming Growth Factor β (TGF β) Uniquely Regulates Production of Glomerular Extracellular Matrix". Appellant asserts that this abstract is consistent with appellant's conception of treating pathologies related to TGFβ-mediated accumulation of extracellular matrix prior to December 22,1988. Appellant submit that because this abstract was presented to clinician attendees of the Nephrology meeting, given Drs. Border and Ruoslahti's medical training, such presentation was in the context of methods of suppressing the deleterious accumulation of TGF-β-induced extracellular matrix and not aimed merely at fulfilling the clinician's attendees' academic curiosity.

Scientific meetings serve a number of purposes including research interests as well as clinical studies for academic and company scientists and physicians.

Appellant asserts without evidence that based upon an in vitro experimental study disclosing the unique role of TGFβ in a kidney cell culture, the ordinary artisan would have extrapolated this finding to reducing extracellular matrix in a wide variety of distinct diseases with TGFβ-specific antibodies.

Given the disclosed uniqueness of TGFβ in a kidney cell culture, it is not readily apparent that the ordinary artisan would extrapolate the role of TGFβ broadly in all instances of the accumulation of extracellular matrix, given the contribution of a variety of factors to distinct conditions and pathologies. Also, the abstract does not mention or discuss methods of inhibiting extracellular matrix accumulation in glomerulonephritis nor the use of TGFβ-specific antibodies as an antagonist either in the context of kidney disease or broadly on any other condition involving the accumulation of extracellular matrix.

Again, appellant asserts that Border and Ruoslahti declare in their Rule 131 Declaration that at the time this abstract was submitted, they had already conceived of using anti-TGF-β antibodies was for their use to inhibit TGF-β in order to decrease deleterious TGF-β-induced production and accumulation of extracellular matrix associated with a pathology or condition, including glomerulonephritis.

Appellant asserts that Exhibit D, a grant proposal laying out experimental aims, and Exhibit E, a publication of results obtained by performing experiments proposed in the grant proposal, speak to appellant's diligence in pursuing the reduction to practice of the claimed methods during the critical period.

Appellant submit that Exhibits D and E must be viewed in context, with Exhibit D being a grant proposal laying out experimental aims and Exhibit E, seven months later, a publication of results obtained by performing experiments proposed in the grant proposal.

Appellant relies upon the excerpt form the Grant Proposal section entitled Specific Aims "to develop regiments for therapeutic intervention in the disease model by antibodies and other agents capable of neutralizing the TGF-β effect. In addition, the Experimental Design and Methods section states the proposal of several experiments "to block or ameliorate the action of TGF-β in the animal model of mesangial injury ... It is conceivable that one or more of these agents could be administered to the animal and/or infused directly into the kidney as therapeutic agents to prevent the expansion of mesangial matrix... We expect that one or more of the agents to be tested will block the action of TGF-β. This information would be immediately applicable to the design of a study to treat humans with glomerulonephritis".

Appellant relies upon Exhibit D corroborates appellant's averments that the reduction to practice of the claimed therapeutic methods were being diligently pursued from prior to December 22, 1988 until the filing date of the priority application and is consistent with appellant's averments in the Rule 131 Declaration.

Appellant also relies upon Exhibit E which are excerpts of an updated draft manuscript, entitled "An Antiserum Against Transforming Growth Factor β Suppresses Experimental Glomerulonephritis" as it existed on August of 1989, which details the experiments proposed in the grant proposal. Appellant submits that the manuscript states that the results achieved in the experimental results with anti-TGF-β treatment warrant the expectation of similar benefits for treatment of human glomerulonephritis with other fibrosis-related diseases.

Here, appellant asserts that the Exhibit E provides documentation that during the critical period appellant were diligently pursuing the reduction to practice of the claimed methods as averred in the Rule 131 Declaration.

Again, it is noted that the priority date of Dasch et al. (U.S. Patent No. 5,772,998) is December 22, 1988, which precedes the dates of both Exhibits D and E.

With respect to species - genus issues, it is acknowledged that where the claims under rejection recite a species and the reference discloses the claimed species, the rejection can be overcome under 37 CFR 1.131 directly by showing prior completion of the claimed species or indirectly by a showing that the claimed species would have been an obvious modification of the species completed by applicant. See In re Spiller 182 USPQ 614 (CCPA 1974).

Appellant acknowledges that Dasch et al. describes the two species of liver cirrhosis and scarring but not adult respiratory distress syndrome. Here, appellant submit that the species is not disclosed in the Dasch et al. patent and therefore is not anticipated by Dasch et al.

Appellant submit that the Rule 131 Declaration itself shows prior invention of the species recited in claims 22 and 25. Here, appellant aver to the conception prior to December 22, 1988, and subsequent diligent reduction to production and deleterious accumulation of extracellular matrix associated with a pathology or a condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti TGF-β antibody. Further, appellant argues that appellant's averments are supported by the Rule 132 Languino Declaration (Exhibit A) and the conference abstract (Exhibit C).

Here, appellant asserts the controlling legal standard articulated by the Ovshinsky Court that it is entirely appropriate for appellant to rely on the averment set forth in the Rule 131 declaration themselves to establish conception of the invention prior to the effective date of the reference.

Appellant submits that in order to antedate a reference that has been cited against an application, distinct requirements exist that depend, in part, on whether the application claims a genus or species, and, in part, on whether the species are disclosed in the cited references.

Regarding genus claim 21, appellant argues that the issue is whether the species described by Dasch et al. would have been obvious to one of ordinary skill in the art in view of what the Appellant's Rule 131 Declarations proves was completed with respect to the invention prior to the effective date of the reference.

Relying upon In re Clarke, 148 USPQ 665 (CCPA 1966), appellant submit that one consideration is this regard is whether it can be shown that appellant had already appreciated that the invention was generic in nature prior to the reference date.

Appellant argues that the Rule 131 Declaration itself shows appellant's appreciation of the generic applicability of their invention to those pathologies and conditions associated with TGF-β-induced production and deleterious accumulation of extracellular matrix in a tissue.

Again appellant rely upon the averments made in the Rule 131 Declaration and in the Languino 132 Declaration as well as the conference abstract.

Appellant maintains that at the time the abstract was submitted, appellant already had conceived of using anti TGF-β antibodies in order to decrease deleterious TGF-β-induced production and accumulation of extracellular matrix associated with glomerulonephritis or other pathologies associated with TGF-β-induced expansion of the extracellular matrix.

With respect to the two conditions not explicitly described in the specification but mentioned in Dasch et al., scleroderma and interstitial lung fibrosis, appellant submit that these conditions are obvious in view of what has been conceived prior to December 22, 1988 by appellant. Again, appellant relies upon the averments in the Rule 131 Declaration. In addition, appellant states that Dasch et al. discloses that scleroderma, like scarring, was known to be a fibrotic disease of the skin and that interstitial lung fibrosis, liked Adult Respiratory Distress Syndrome was known to be fibrotic disorder of the lung. Appellant submit that given their prior conception of a generic method of decreasing the TGF-β-induced production of and deleterious accumulation of extracellular matrix associated with a pathology or a condition, appellant possess so much of the invention as to encompass the Dasch et al. patent.

Regarding Species Claims 23 and 25, appellant asserts that in order to antedate a reference that has been cited against an application, distinct requirements exist that depend, in part, on whether the application claims a genus or species and, in part, on the species disclosed in the cited references. Consequently, claims 21-23 and 25 must be separately examined with regard to whether appellant have made the necessary showing for prior invention of the claimed subject matter It is for this reason, claim 21, directed to a genus, and claims 22, 23, 25 and if entered, claim 35 each directed to distinct species, do not stand or fall together.

It is noted that Rule 131 Declaration itself does not discuss the obviousness of species. For example, the Rule 131 Declaration does not state that scleroderma, like scarring, was known to be a fibrotic disease of the skin and that interstitial lung fibrosis, liked Adult Respiratory Distress Syndrome was known to be fibrotic disorder of the lung.

For the reasons set forth herein, appellant submit that the Rule 131 Declaration of March 15, 2001 is sufficient to antedate Dasch et al. In both the rejections under 35 USC 102(e). and 103(a)..

In addition to the above-mentioned, the following rebuttal is provided.

While appellant has provide evidence/Exhibits to indicate prior conception to the prior art as it would read on Dasch et al. (U.S. Patent No. 5,772,998) appellant has not provided sufficient objective evidence to establish acts in this country commensurate in scope with the claimed invention.

Here, it is noted that the priority date of Dasch et al. (U.S. Patent No. 5,772,998) is December 22, 1988 and that the priority dates of Ruoslahti et al. (U.S. Patent No. 5,583,103) and Bassols et al. (J.Biol. Chem. 263: 3039-3045, 1988) are more than one year prior to applicant's priority date.

The statements of stated goals in the Rule 131 Declaration and the Languino 132 Declaration appear to be the only sources for the "stated goals" of reducing the deleterious accumulation of extracellular matrix associated with the scope of pathologies or conditions, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti-TGF-β antibody.

Other than the Rule 131 and 132 Declarations, neither Appellant or Languino have provided any corroborating factual evidence to support the "stated goals" using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix associated with a disease, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scarring, by contacting the affected tissued with anti- TGF-β antibody.

The affidavit or declaration must state FACTS and produce such documentary evidence and exhibit in support thereof as are available to shoe conception and completion of invention in this country, at least conception being at a date prior to the effective date of the references. See MPEP 715.07 and 715.07(c).

A general allegation that the invention was completed prior to the date of the reference is not sufficient. Ex parte Saunders, 1883 C.D. 23, 23 O.G. 1224 (Comm'r Pat. 1883). Similarly, a declaration by the inventor to the effect that his or her invention was conceived or reduced to practice prior to the reference date, without a statement of facts demonstrating the correctness of this conclusion, is insufficient to satisfy 37 CFR 1.131. See MPEP 715.07.

37 CFR 1.131(b) requires that original exhibits of drawings or records, or photocopies thereof, accompany and form part of the affidavit or declaration or their absence satisfactorily explained. See MPEP 715.07.

Appellant's reliance on "stated goals" in the Rule 131 and 132 Declarations is critical in supporting the generic claims as well as the claimed species. However, there is no corroborating objective evidence that provides for using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix associated with a disease, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scarring, by contacting the affected tissued with anti- TGF-β antibody. These are mere statements that do not provide a clear information the nature or time of the discussing the stated goals. For example, appellant's reliance on the other evidence never mention adult respiratory distress syndrome, cirrhosis of the liver and scarring. If the stated goals were intended to be broad, one would reasonably expect that these other pathologies and conditions would have been mentioned in the supporting evidence/ Exhibits, such as grant proposals and manuscripts.

There is insufficient objective corroborating evidence to support the "stated goals", as asserted in the Rule 131 and 132 Declarations.

For example, the Languino was asked to assist in preparing anti TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracelluar matrix associated with a disease, including kidney disease. See Languino 132 Declaration (Exhibit A).

Appellant in conjunction with Languino rely upon Animal Usage Form, wherein the Project Goals are to produce quantities of anti-human TGF-β cyclized peptide for use in kidney disease research, wherein rabbits were immunized to produce high quality antiserum which can be used for identification of TGF-β in tissue samples and in vitro assays to study progression of kidney injury. See Animal Usage Form (Exhibit B).

Therefore, Animal Usage Form provides for generating anti -TGF-β antibody for in vitro kidney disease research. There does not appear sufficient direction or recognition that these in vitro research studies would lead to reducing the deleterious accumulation of extracellular matrix associated with the scope of pathologies or conditions, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti TGF-β antibody.

The Languino 132 Declaration does not appear to provide sufficient direction or recognition that the in vitro research studies cited in the Animal Usage Form would lead to reducing the deleterious accumulation of extracellular matrix associated with the scope of pathologies or conditions, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti TGF-β antibody.

The laboratory notebook pages from Languino's notebook set forth protocols for immunizing rabbits with TGF-β. See Exhibit B.

Similar to the Animal Usage Form and the Languino 132 Declaration, the laboratory notebook pages do not appear to provide sufficient direction or recognition that the immunization procedures nor the in vitro research studies cited in the Animal Usage Form would lead to reducing the deleterious accumulation of extracellular matrix associated with the scope of pathologies or conditions, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti TGF-β antibody. Although the in vitro research studies may have indicated the role of TGF-β in extracellular matrix accumulation in kidney cells, there appears insufficient evidence that one of ordinary skill in the art would have necessarily extrapolated that the production of producing a rabbit antiserum for such in vitro research studies would have led to the use of therapeutic antibodies in the treatment of human diseases and conditions.

With respect to the conference abstract entitled "TGF-β is unique among growth factors in its metabolic effect on glomerular ECM" that the release of TGF-β could stimulate the expansion of ECM and progression to glomerulosclerosis. See Abstract of December 11-14, 1988.

Here, appellant asserts that given their medical training as physicians, they already conceived of using anti TGF-β antibodies in order to decrease deleterious TGF-β-induced production and accumulation of extracellular matrix associated with other pathologies associated with TGF-β-induced expansion of extracellular cell matrix.

Here again, there is no statement in the conference abstract about the scope of pathologies or conditions, including adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti TGF-β antibody.

With respect to glomerulonephritis, the conference abstract discloses that TGF-β is unique among growth factors in its metabolic effects on glomerular extracellular matrix. The release of a substance like TGF-β in glomerulonephritis could stimulate the expansion of extracellular matrix and mediate the progression to glomerulosclerosis.

However, the conference abstract does not of treating reducing the deleterious accumulation of extracellular matrix associated with the scope of pathologies or conditions, including adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti -TGF-β antibody. Rather, this conference abstract is drawn studying the role of growth factors such as TGF-β in the progression of glomerulonephritis.

With respect to therapy, the Grant Proposal discloses the production of neutralizing antisera and it is conceivable that one or more of these agents could be administered to the animals and/or infused directly into the kidney as therapeutic agents to prevent the expansion of the mesangial matrix. See Grant Proposal, Background and Significance, Section B(e); see Exhibit D. The Grant Proposal expects that one or more of the agents to be tested will block the action of TGF-β, wherein the information would be applicable to the design of a study to treat humans with glomerulonephritis. The objective of the proposed studies was to test the hypothesis that growth factors such as TGF-β regulates the production and accumulation of extracellular cellular matrix in glomerular disease (see the last sentence of Section A Specific Aims).

Therefore, the Grant Proposal (January 1989) which was subsequent to the December 22, 1998 priority date of Dasch et al. (U.S. Patent No. 5,772,998) and is directed to testing the hypothesis relating to the role of TGF-β in regulating the production and accumulation of extracellular matrix in glomerular disease in order to design treatments for humans.

The Grant Proposal does not disclose treating reducing the deleterious accumulation of extracellular matrix associated with the scope of pathologies or conditions, including adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti TGF-β antibody.

Appellant relies upon excerpts of an undated draft manuscript (August 1989) entitled "An Antiserum Against Transforming Growth Factor β Suppresses Experimental Glomerulonephritis", which contains the in vivo protocol corresponding to Example VII of the instant specification.

Here, the results contribute to the understanding of the pathogenesis of experimental nephritis and suggest a new form of therapy for glomerulonephritis with anti-TGF-β antibody (see Abstract and page 5, paragraph 2). Further, page 5, paragraph 2 of the manuscript discloses encouragement one to expect similar potential benefits in human glomerulonephritis and perhaps in other disease as well were fibrosis is a factor.

The draft manuscript discloses potential benefits of treatment of human glomerulonephritis with an anti-TGF-β antibody and does not disclose the scope of pathologies or conditions, including adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti TGF-β antibody.

Both the Grant Proposal and the draft manuscript are directly only at glomerulonephritis and testing the hypothesis of treating glomerulonephritis with an agent such as anti-TGF-β antibody.

Other than the Rule 131 Declaration, appellant has not provided any objective evidence to support prior conception, diligence and reduction of practice of reducing the deleterious accumulation of extracellular matrix associated with the scope of pathologies or conditions, including adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti TGF-β antibody.

Further, with respect to the evidence that precede the December 22,1988 priority date of Dasch et al.; there is no objective evidence that the ordinary artisan would recognize the reliance on the Animal Usage Form, where the Project Goals of producing anti-human TGF-β cyclized peptide for use in kidney disease research (Animal Usage Form; Exhibit B) and on the conference abstract, which discloses that TGF-β is unique among growth factors in its metabolic effects on glomerular extracellular matrix would read on methods of reducing the deleterious accumulation of extracellular matrix associated with the scope of pathologies or conditions, including adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti TGF-β antibody.

In contrast to appellant's reliance on Languino's statement of "associated with a disease, including kidney disease" (Languino 132 Declaration), "associated with a disease" does not provide sufficient direction nor support for methods of reducing the deleterious accumulation of extracellular matrix associated with the scope of pathologies or conditions, including adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti TGF-β antibody.

Diseases and conditions such as the claimed glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scaring as well as the interstitial lung fibrosis and scleroderma as disclosed by Dasch et al. are distinct because the pathological conditions differ in etiologies and therapeutic endpoints. For example, these diseases and conditions encompass different tissues and organs as well as etiologies and therapeutic endpoints.

Appellant has not provided objective evidence that the ordinary artisan would have recognized that the production of TGF-β antibody and in vitro assays on the role of TGF-β in mesangial cultures conducted by appellant prior to December 22,1988 as well as the abstract, grant proposal and draft manuscript on determining the contribution of TGF-β in experimental nephritis would read broadly on diseases and conditions with varying etiologies and therapeutic endpoints, such as the claimed glomerulonephritis, cirrhosis, adult respiratory distress syndrome and scarring.

Appellant rely upon In re Ovshinsky to indicate that exhibits accompanying the Rule 131 Declaration need not support all of the claimed limitations inasmuch as missing feature may be supplied by the declaration itself. In the instant application, the only support for methods of reducing the deleterious accumulation of extracellular matrix associated with the scope of pathologies or conditions, including adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti-TGF-β antibody is the asserted "stated goals" in the Rule 131 Declaration. There is no corroborating objective evidence prior to nor subsequent to the December 22, 1988 priority date of Dasch et al. to support the claimed diseases of adult respiratory distress syndrome, cirrhosis of the liver and scarring nor that these diseases were obvious modifications of testing the role of TGF-β in experimental in vitro mesangial cultures or in vivo murine nephritis models. There is no corroborating evidence to support the asserted " stated goals" in the Rule 131 Declaration to encompass claimed diseases of adult respiratory distress syndrome, cirrhosis of the liver and scarring.

Even with respect to treating glomerulonephritis which was the focus of appellant's Exhibits, it is noted that the Animal Usage Form and the conference abstract that precede the December 22, 1988 priority date of Dasch et al. are limited to studies of determining the presence or role of TGF-β in mesangial cultures, as an in vitro model of glomerulonephritis. While the role of TGF-β in mesangial cultures was tested prior to December 22, 1988, the use of anti-TGF-β antibody in experimental in vitro mesangial cultures or in vivo murine nephritis models had not been conducted prior to December 22, 1988. Border's Grant Proposal as well as draft manuscript are couched in terms of potential benefits to treating human glomerulonephritis with some agents.

Again, with respect to filing declarations under 37 CFR 1.131, the showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from said date to a subsequent reduction to practice or to the filing of the application. Original exhibits or drawings or records or photocopies thereof must accompany and form part of the affidavit or declaration or their absence satisfactory explained. See MPEP 715.07.

While appellant asserts that exhibits and declarations are not required, Rule 131 clearly requires supporting documentation to the Rule 131 Declaration or a satisfactory explanation to explain their absence.

Appellant has not provided a sufficient explanation as to why their is not supporting evidence for the stated goals for methods of reducing the deleterious accumulation of extracellular matrix associated with the scope of pathologies or conditions, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scaring by contacting the affected tissued with anti-TGF-β antibody.

Further, the evidentiary evidence prior to December 22, 1988 appears drawn to determining the contribution of TGF-β to extracellular matrix accumulation in mesangial cultures as a model of glomerulonephritis and not necessarily to the treatment of glomerulonephritis with anti-TGF-β antibody or broadly to the inhibition of extracellular matrix in various pathologies and conditions.

Subsequent to December 22, 1988, the Border Grant Proposal and co-authored draft manuscript appear to draw on experimental in vivo models to test agents that may be useful in treating glomerulonephritis. Again, these documents do not mention the inhibition of extracellular matrix in various pathologies and conditions such as cirrhosis, scarring and adult respiratory distress syndrome.

With respect to appellant's arguments on genus - species claim limitations, it is noted that generic claim 21 recites "a method of decreasing the deleterious accumulation of extracellular matrix associated with a pathology or a condition wherein TGF-β-induced production and delerterious accumulation of extracellular matrix comprising contacting the tissue with an anti-TGF-β antibody that bind to TGF-β".

However, appellant was not in possession of the generic invention prior to the effective date or activity of the prior art. The Rule 131 Declaration and corroborating evidence does not provide the minimum disclosure required for the given scope of "pathologies and conditions" to antedate the prior art. A reference or activity which discloses several species of a claimed genus can be overcome directly under 37 CFR 1.131 only by a showing the appicant completed, prior to the date of the reference or activity, all of the species shown in the reference. In re Stempel, 113 USPQ77 (CCPA 1957). See MPEP 715.03(B).

Given the scope as well as the recitation of "pathology and condition" recited in the independent claim as well as the dependent claims, the claims are not simply directed toward suppressing the activity of "the deleterious accumulation of TGF-β-induced extracellular matrix in the tissue". Rather, the recitation fo "pathology and condition" clearly indicates the context of multiple diseases or condition and determining which ones (or at least a representative number of species) are relevant or appropriate to the ordinary artisan.

Again, both appellant and examiner have prosecuted the claims as if they stood or fell together. The only issue of record has been whether appellants' Declaration under 37 C.F.R. 1.13, filed on March 15, 2001 was sufficient to antedate U.S. Patent No. 5,772,998. Appellant did not appear to distinguish the genus and species claims prior to this Appeal Brief.

While appellant has provided some documentary support as evidence of conception, diligence and reduction to practice; these documents or exhibits together with the comments in the Border/Ruoslahti declaration are not clear on their face as they read on conception, diligence and reduction to practice commensurate in scope with the claimed methods in order to antedate the prior art. Appellant has the burden to explain the contents of the pages as proof of acts amounting to conception, diligence and reduction to practice. See In re Borkowski and Van Venrooy 184 USPQ 29 (CCPA 1974). Absent a clear explanation of pointing out exactly what facts were established and when they were established and relied upon by appellant, the Rule 131 and 132 Declarations and Exhibits provide insufficient assistance in enabling the PTO to determine applicant's assertions of conception, diligence and reduction to practice before the prior art as it reads on methods of decreasing the deleterious accumulation of extracellular matrix associated with pathologies and conditions, including glomerulonephritis previous to the effective dates of the prior art references.

(12) For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
June 3, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
conferee